A I D S TREATMENT N E W S

Issue Number 416
Oct./Nov., 2005

Published 12 times a year by
John S. James
AIDS Treatment News
1233 Locust St., 5th floor
Philadelphia, PA 19107

Contents

AIDS Treatment News

Subscription and Editorial Office:
AIDS Treatment News
Philadelphia FIGHT
1233 Locust St., 5th floor
Philadelphia, PA 19107
800-TREAT-1-2 toll-free U.S. and Canada
fax: 215-985-4952
email: aidsnews@aidsnews.org
web: http://www.aidsnews.org

Editor and Publisher: John S. James

Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

Subscription Information: Call 800-TREAT-1-2

Business/Commercial: $325/year.

Nonprofit community organizations: $150/year.

Individuals: $140/year, or $80 for six months.

Special discount for persons with financial difficulties: $54/year, or $30 for six months. If you cannot afford a subscription, please write or call.

Back issues, and discounts for multiple subscriptions, are available; contact our office for details.

Please send U.S. funds: personal check or bank draft, international postal money order, or travelers' checks. VISA, Mastercard, and purchase orders also accepted.

To protect your privacy, we mail first class without mentioning AIDS on the envelope, and we keep our subscriber list

Special Tax Break for Major Donors to Charities -- Only Through December 31

by John S. James, *AIDS Treatment News*

"For outright gifts of cash made between August 28, 2005, and December 31, 2005, to charities, individuals may take a federal income tax deduction of up to 100 percent of their adjusted gross income (AGI). On January 1, 2006, the deduction limit will revert back to 50 percent of AGI." [1]

This applies for donations to charities -- but not to donor-advised funds or private foundations. [1]

Comment

Apparently this provision (of the Katrina Emergency Tax Relief Act of 2005) only

helps those who can afford to donate more than half of their income to charities (*not* limited to hurricane relief). It appears to let people with plenty of assets to live on wipe out their income tax entirely for 2005, by giving their whole taxable income to the charities of their choice. Check with your accountant for an authoritative opinion.

Fundraisers and donors should know about this possibility before it expires on December 31. Spread the word.

Reference

1. Harvard University, http://post.harvard.edu/pgo/

TMC125: New Results, Large Phase III Trial Begins

by John S. James

TMC125 (also spelled TMC-125, TMC 125, or etravirine), by Tibotec Pharmaceuticals Ltd., based in Cork, Ireland and now part of Johnson & Johnson, is a "second generation" NNRTI (non-nucleoside reverse transcriptase inhibitor) -- an antiretroviral in the same class as efavirenz (brand name Sustiva, or Stochrin in many countries) or nevirapine (Viramune). It differs from these in being much less susceptible to viral resistance. This is not an accident; the drug molecule was carefully designed to be able to "wiggle and jiggle" so that it can change its shape in order to fit into the active pocket of the HIV enzyme reverse transcriptase and stop the enzyme from working, even when that pocket changes shape (due to resistance mutations) so that efavirenz and nevirapine will not fit. For example, the highly treatment experienced volunteers who entered the phase II trial named TMC125-C223 (reported in mid November at the 10th European AIDS Conference) had HIV that was on the average about 40 times less sensitive to efavirenz when they started the trial, and about 60 times less sensitive to nevirapine, but only 1.6 times less sensitive to TMC125.

In the 24-week data presented at the conference [1], those on combination antiretrovirals including the lower of two doses of TMC125 had a 1.04 log drop (to slightly less than 10% of the amount of virus they started with) in HIV viral load; those on the higher dose had a 1.18 log drop. These were compared with an "active control" group -- volunteers who got the best regimen that could be devised for them using approved drugs. The active control had a 0.19 log drop, (not statistically significant). This group did show a modest improvement earlier in the 24 weeks, as much as half a log, probably because of the switch to a regimen carefully designed for them at that point in time.

The size of the viral load drop from TMC125 depended very much on having other active drugs in the regimen. Those with no other active drug (because they were resistant to all the other drugs in their regimen) averaged only about a half-log drop (average of the two TMC125 doses). Those whose virus was sensitive to one antiretroviral in addition to TMC125 had an average one-log drop or a little less; those sensitive to two other antiretrovirals averaged about one and a half logs HIV reduction, or a little more.

Note: As this article went to press we learned that one phase II trial, TMC125-C227, is being stopped early. This trial tested TMC125 in volunteers who had received an NNRTI (usually efavirenz or nevirapine) and had at least one resistance mutation to it. The trial was stopped because some of these volunteers had a poor antiviral response to TMC125; those in the control group, who were treated with protease inhibitors instead, did better in reducing viral load. The new phase III trials -- which use a different formulation of TMC125 with a different group of patients -- have not been changed. The C227 trial was being conducted in eight

countries, not including the U.S. We will be watching for more information on what happened in this discontinued trial.

Two Phase III Trials Starting

On November 17, 2005 Tibotec announced the start of two phase III "pivotal" trials with 600 heavily treatment experienced patients each, to be conducted in 18 countries. These trials are unusual in combining two experimental drugs. TMC125 will be combined with TMC114, a new protease inhibitor also from Tibotec. These similar trials are called DUET 1 (official name TMC125-C206) and DUET 2 (TMC125-C216).

For more information about these (or other) clinical trials in the U.S, see http://www.clinicaltrials.gov; search for "TMC125" (quotation marks not necessary).

References

1. Nadler JP, Grossman HA, Hicks C, and others. Efficacy and tolerability of TMC125 in HIV patients with NNRTI and PI resistance at 24 weeks: TMC125-C223. 10th European AIDS Conference/EACS, November 17-20, 2005, Dublin, Ireland [abstract LBPS3/7].

Integrase Inhibitors: First Clear Success in Human Trial

by John S. James

Merck reported that its experimental integrase inhibitor MK-0518 reduced HIV viral load 98%, in a 10-day monotherapy trial in 28 treatment-naive volunteers. [1] All doses tested, from 100 to 600 mg taken as tablets twice daily, showed a highly statistically significant viral reduction (p=0.001). There were no serious adverse effects in this trial, and no one discontinued the drug due to adverse effects. Based on these results, a 48-week dose-ranging trial of MK-0518 has been started in antiretroviral-naive patients. This information was presented November 18 at the EACS (European AIDS Clinical Society) meeting in Dublin, Ireland.

Background

HIV uses at least three enzymes to reproduce -- reverse transcriptase, protease, and integrase. These enzymes are obvious targets for designing anti-HIV drugs that block them (but enzymes are certainly not the only targets; there are many more steps in the HIV life cycle that drugs might attack). AZT and many other approved drugs block reverse transcriptase. Protease inhibitors came into use around 1996 and revolutionized AIDS treatment (although highly effective HAART combinations without protease inhibitors are also possible). Integrase inhibitors have been the hardest to develop, partly because different protease inhibitors were already used in other areas of medicine, while anti-HIV integrase inhibitors had to be developed from scratch. An earlier integrase inhibitor, S-1360, developed by Shionogi & Co. and GlaxoSmithKline, had to be discontinued because of poor bioavailability.

The new Merck trial clearly shows that an integrase inhibitor can work in people to lower HIV viral load.

For More Information

Information about this drug will change rapidly, and we do not know which Web or other information will be best. You might check first with the treatment-information sources you already use.

For general news you might try http://news.google.com/ -- search for "integrase" (quotation marks not necessary). Or for more focus on AIDS-related news, try http://www.aegis.org/search/ -- "integrase" returns hundreds of articles, mostly very technical, so try "MK-0518" (or any newer drug name that Merck may use in the future).

References

1. Morales-Ramirez J.O., Teppler H., Kovacs C., and others, Protocol 004 Team (USA, Canada, Australia). Antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in ART-naive HIV-1 infected patients. 10th European AIDS Conference / EACS, November 17-20, 2005, Dublin, Ireland [abstract # LBPS1/6].

CCR5 Entry Inhibitor Problems: No Clear Answers Yet

by John S. James

Three different experimental drugs that inhibit HIV by the same mechanism (blocking its use of the CCR5 co-receptor) have run into problems recently in clinical trials. But the problems are very different.

CCR5 is a protein on the surface of human cells that most HIV uses to help it enter the cell (some HIV uses a different protein instead, usually CXCR4). A few people have no CCR5 (due to an inherited mutation); they appear to be in good health, and are very unlikely to be infected with HIV. Therefore scientists have looked for CCR5 antagonists -- drugs that could bind to CCR5 and prevent HIV that uses CCR5 from entering cells.

Two risks with this treatment approach are that the CCR5 may turn out to be necessary for some people for unknown reasons -- or that when HIV is prevented from using CCR5, it might evolve within an individual patient to use CXCR4 instead. At this time no one knows if either of these will be a problem.

Three CCR5 entry inhibitors have recently been in large clinical trials: aplaviroc from GlaxoSmithKline, maraviroc from Pfizer, and vicriviroc from Schering Plough.

Here is the basic situation (early December 2005).

Aplaviroc: On October 25, 2005, GlaxoSmithKline announced that it was stopping enrollment in its phase III trials after potentially serious liver toxicity had been found in several patients in this and other trials. Patients already in the phase III trial will be allowed to continue under careful monitoring until other plans can be made, if their physician believes they are benefiting from the drug, but Glaxo's intent is to have all patients stop therapy with aplaviroc.

Maraviroc: One patient of more than one thousand who have received maraviroc developed serious liver toxicity. Currently no one knows if maraviroc contributed to the problem, because this patient had other risk factors and had elevations of liver enzymes before starting the drug. Only five doses of maraviroc were taken (the liver problems with aplaviroc took much longer to develop). The DSMB (Data Safety Monitoring Board) analyzed the trials in July and late September and recommended no changes. It met on an ad-hoc basis to analyze this case, and recommended several changes to study eligibility criteria and safety monitoring, which are now being implemented. The DSMB will next meet as scheduled in January.

Vicriviroc: Schering-Plough and the ACTG stopped low-dose arms in their trials, and later Schering-Plough stopped its treatment-naive trial entirely, because the volunteers receiving vicriviroc plus Combivir were not controlling the virus as well as those in a comparison arm receiving efavirenz plus Combivir. Trials for antiretroviral-experienced volunteers are continuing (see http://www.clinicaltrials.gov - search for "vicriviroc"). We have not heard of liver toxicity or other safety problems.

The FDA, working with the Forum for Collaborative HIV Research, had set a public meeting in January on long-term followup of patients enrolled in these trials. On December 1 the FDA announced that this meeting, the FDA/FCHR Collaborative Meeting on Long-Term Safety Concerns Associated with CCR5 Antagonist Development, would be postponed until February or March, in order to wait for more information. Comments will be accepted until January 15 at http://www.hivforum.org/CCR5/index.html

Comment

The above information does not suggest a "class effect" -- that blocking CCR5 itself will cause problems, no matter what drug is used to do so. However, no one knows why natural selection has led to over 99% of people having CCR5 -- but with the others having no obvious ill health as a result. Some published research has suggested that removing CCR5 in animals, while not causing problems just by itself, can make certain other problems more serious. All this is guesswork until more information is available.

We are concerned that due to recent waves of publicity and lawsuits about the dangers of other, non-HIV drugs, companies may be too ready to abandon experimental treatments if problems develop. The alternative is to see if it is possible to manage problems that may affect very few patients -- by detecting them early enough to prevent harm, or better yet, by learning the mechanisms of toxicity well enough to predict who is likely to be vulnerable, so that they will never take the drug but use other treatment options instead. Such practical, focused medical research could have spin-off benefits for treating other diseases as well.

The problem is that neither academic nor pharmaceutical research groups are in a particularly good position to do this work, given how U.S. industry is organized today. Some team or teams would need to specialize in such investigations, probably for a number of different drugs, and find modest but long-term funding to do so. Dealing with "rights" to the various chemicals and research tools owned by many different parties could also be a serious obstacle to producing useful results.

Failure of Tenofovir + Abacavir + 3TC Combination; Full Report Published, More Insight

by John S. James

In 2003 researchers stopped a clinical trial abruptly when they found that a combination of three drugs that seemed likely to work well together failed to control the virus in many patients, and led to a very high rate of viral resistance; a comparison regimen that used efavirenz instead of the tenofovir worked well. A similar combination (tenofovir plus abacavir plus ddI) also failed. However, regimens that include AZT do not fail in this way. The problem was completely unexpected, and since it occurred, several different theories were proposed.

No one knows the answer for sure -- and we will probably never know, since it would be unethical to test the failed triple combinations in patients with HIV. But many researchers now believe the most likely explanation is that the drug combinations failed to control the virus because of a low genetic barrier to HIV resistance. Two mutations that developed in this trial protect the virus against the three drugs.

The December 1, 2005 *Journal of Infectious Diseases* published the full report of the trial [1] and a commentary [2]; both are available free online.

"The most likely explanation is the low genetic barrier to resistance produced by synergistic selection pressure from all 3

drugs for 2 point mutation, M184V and K65R. Both abacavir and tenofovir DF select for the K65R mutation, which reduces susceptibility to both drugs, as well as to lamivudine [3TC]. M184V is selected for by lamivudine and abacavir, and it decreases susceptibility to both. Thus, the selection of 2 mutations, each of which may preexist as minority species, leads to virologic failure with this regimen." [1]

The authors conclude that physicians should not try new combinations on their own as the first antiretroviral treatment for patients. "Given the growing number of potent, well-studied combinations now available, there is no longer a rationale for the use of untested regimens outside of clinical trials in the treatment of therapy-naive HIV-infected patients." [1]

References

Note: Both articles below were made available free online by the journal; you do not need to be a subscriber. They are available through the Table of Contents of the December 1 issue,
http://www.journals.uchicago.edu/JID/journal/contents/v192n11.html

1. Gallant JE, Rodriguez AE, Weinberg WG, and others, for the ESS30009 study. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *Journal of Infectious Diseases.* December 1, 2005; volume 192, pages 1921-1930.

2. Kuritzkes DR. Less than the sum of its parts: Failure of a tenofovir-abacavir-lamivudine triple-nucleoside regimen. Editorial commentary. *Journal of Infectious Diseases.* December 1, 2005; volume 192, pages 1867-1868.

XVI International AIDS Conference, August 2006 in Toronto; Deadlines Approaching;

Reduced Registration Fees

The big international AIDS conference that happens every even-numbered year will take place August 13-18 in Toronto, Canada. The theme of the 2006 conference is "Time to Deliver." Everyone interested should know that important deadlines are coming up.

February 22, 2006 is the deadline for submitting all abstracts (except late breakers, which must include newly available information, and even so are less likely to be accepted; late breaker abstract submission opens May 29 and closes June 12). All abstracts must be submitted online.

February 22 is also the deadline for the lowest registration fees: $550 for regular delegates from non-OECD countries (these prices are in U.S. dollars), $750 from OECD (a group of 30 mostly-rich countries). Student/youth (under age 26 as of August 13) and accompanying-person fees are much less. Regular registration fees go up after February 22, and all fees go up after May 15. The conference is still too expensive but this is a significant reduction, and conference organizers plan to increase scholarship support by 20%.

February 22 is also the deadline for applying for a scholarship.

March 15 is the deadline for applying to the Global Village, "the only Conference space open to Conference delegates, non-governmental organisations, AIDS service organisations, the media, activists and the general public." For more information visit http://www.aids2006.org/subpage.aspx?pageId=367 -- or look for a link on the home page.

March 15 is also the deadline for applying for the Cultural Activities Program, involving art and AIDS.

Canadian visa, other requirements: Travelers are strongly advised to check visa requirements for their country "as soon as they are thinking about attending the Conference," and start applying at least eight to 12 weeks before the August

13 start. (Citizens of the U.S. and about 40 other countries do not require a visa. For U.S. citizens, a U.S. passport is the recommended identification -- some other identification can be accepted in Canada, but make sure it will get you back into the U.S. as well). Anyone with a "criminal background" must apply as soon as possible to get necessary documentation in time. The visa application no longer requires disclosure of HIV or other medical diagnoses, except tuberculosis of the lung. More information can be found on the Conference Web site.

We do not know if people with HIV will have trouble changing planes in the U.S., due to its exclusion of visitors with HIV -- or if this depends on whether it is necessary to go through U.S. customs when changing planes. A direct flight to Canada may be best. Check the Web site below for any other information.

For more information on these and many other aspects of the conference, including a complete list of key dates, visit http://www.aids2006.org

AIDS Vaccine History on PBS Documentary; DVD, Book Available

"Ending AIDS: The Search for a Vaccine", an excellent 56-minute documentary history of AIDS vaccine research narrated by Richard Gere, will be shown on PBS in December 2005; check local stations for scheduled times.

The book *Shots in the Dark: The Wayward Search for an AIDS Vaccine*, by science writer Jon Cohen, inspired the documentary, which tells the story with historical footage along with recent interviews with experts.

The video is also available on DVD for $24.95, and a companion book to the program for $15.95. For more information, visit
http://www.pbs.org/endingaids/

C2EA (Campaign to End AIDS): Statewide Organizing after the November Caravans

by Suzy Subways

Eight caravans of people with HIV and their allies traveled cross-country to Washington, D.C., for the Campaign to End AIDS' (C2EA) four days of action November 5 to 8. Organizers say about 500 people made the journey, including 50 who walked from New York City, and thousands attended events organized by C2EA and local communities along the way. Charles King, CEO of the New York City-based AIDS organization Housing Works, says the goal was to build a national movement with strength in small towns and throughout the country, including the South and the Midwest as well as the coasts. "We need to harness the energy we've built for the last 11 months, and solidify it at the level of states and territories," he says. "The next step is state-wide coalitions in all 50 states, Puerto Rico and Washington, D.C."

The four days of action kicked off with a march through DC's Anacostia neighborhood, instead of the protest-as-usual option of taking it to the Mall or another landmark, ignoring the local reality of America's highest HIV rate. African-American residents welcomed the protesters, who were mostly people of color themselves, and asked for information. "This demonstrates the hard work of grassroots organizing at its best -- which has been cast aside," said Sean Strub, founder of POZ magazine, at the march. He emphasized the lack of support from major AIDS institutions, many of which have few HIV positive board members. "People with HIV have to be at the table at all levels," he said.

King says C2EA is currently revamping its steering committee, which will be made up of representatives from statewide coalitions. "Each state and territory has to go through an organizing process and turn over a C2EA web page, and democratically